# Pitfalls in the assessment of gestational transient thyrotoxicosis

Review

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## Abstract

Gestational transient thyrotoxicosis (GTT) is associated with direct stimulation of the maternal thyroid gland by human chorionic gonadotropin (hCG). It is characterized by slightly higher thyroid hormone and lower thyroid-stimulating hormone (TSH) levels in early pregnancy and mild or no symptoms. While GTT must be distinguished from Graves' disease (GD), which is associated with maternal and fetal complications, treated GD and new-onset GD in pregnancy are occasionally challenging to distinguish. Evaluating serum hCG levels and TSH receptor antibody (TRAb) titers can help, but the results are not irrefutable due to pregnancy-related immunosuppression. Moreover, GTT can follow unusual clinical courses in relation to some pregnancy complications. Excessive hCG production can cause severe GTT symptoms in patients with hyperemesis gravidarum, trophoblastic disease, or multiple pregnancies. Thyrotoxicosis can emerge beyond the second trimester in patients with gestational diabetes mellitus and mirror syndrome, because of delayed elevations in the hCG levels. Detailed knowledge about GTT is necessary for correct diagnoses and its appropriate management. This review focuses on the diagnosis of GTT, and, particularly, its differentiation from GD, and unusual clinical conditions associated with GTT that require comprehensive management.



**Keywords:** gestational transient thyrotoxicosis; Graves' disease; human chorionic gonadotropin; pregnancy; thyroid-stimulating hormone receptor antibody

## Introduction

Pregnancy profoundly affects the thyroid gland and thyroid function. Hyperthyroidism during pregnancy is rare, but given the adverse outcomes that can occur in the mother and the fetus, identifying hyperthyroidism is essential [1]. Graves' disease (GD) occurs in 0.1–1% of all pregnancies and is the most common cause of hyperthyroidism during pregnancy [2,3]. In contrast, gestational transient thyrotoxicosis (GTT), which is characterized by increased thyroid hormone levels and thyroid-stimulating hormone (TSH) suppression during normal pregnancies, causes thyrotoxicosis more frequently than GD. GTT occurs in 2–11% of all pregnancies [4]. As other causes of thyrotoxicosis during pregnancy are rare, the differential diagnosis is usually GD or GTT [5]. However, as the symptoms and signs of hyperthyroidism can be seen in normal pregnancies, diagnosing hyperthyroidism that presents for the first time in pregnancy can be challenging. While GTT usually has a short duration and resolves spontaneously [6,7], it can be associated with unusual manifestations, including a delayed onset, severe symptoms requiring specific treatments, or a prolonged course [8]. This review focuses on diagnosing GTT, and, particularly, its differentiation from GD, and unusual clinical conditions associated with GTT that require comprehensive management.

## Overview of gestational transient thyrotoxicosis

Kimura et al. [9] were the first to describe 'gestational thyrotoxicosis', and it was characterized in pregnant women as follows: symptoms of thyrotoxicosis during early pregnancy, marked increases in free thyroxine (FT4) and free triiodothyronine (FT3)

levels, complications associated with hyperemesis gravidarum (HG), spontaneous recovery during the latter half of pregnancy, negative antithyroid autoantibodies, the absence of a goiter, and circulating human chorionic gonadotropin (hCG) with high levels of biological activity. However, the clinical manifestations of GTT are not always evident [6]. Given that GTT symptoms are similar to those seen during normal pregnancies, GTT is under-diagnosed, and it is challenging to detect without assessing thyroid function [6]. The pathological mechanisms that contribute to GTT include thyrotropic stimulation of the thyroid gland by placental hCG [10], dysregulation of hCG production, hypersensitivity of the TSH receptor to hCG [8], and heightened sensitivity of the thyroid gland to thyroid hormone stimulation [11]. Strong positive correlations are evident between the serum FT4 and hCG levels during the first trimester [4,12]. The serum hCG levels rise soon after fertilization and peak at 10–12 weeks of gestation, and when they peak, the serum TSH levels fall (Figure 1) [13]; the TSH levels were suppressed in 67% of women with hCG levels >200,000 IU/L and in 100% of women with hCG levels >400,000 IU/L [14,15]. Increases in serum thyroxine-binding globulin (TBG) levels caused by a reduced TBG clearance as consequences of estrogen and hCG-induced TSH receptor stimulation, greatly affect thyroid function during pregnancy [16].

Alpha and beta subunits comprise the glycoprotein hCG. The alpha subunit is almost identical to those found in TSH, luteinizing hormone, and follicle-stimulating hormone [13]. The beta subunits of hCG and TSH share an 85% sequence homology in the first 114 amino acids and they contain 12 cysteine residues at highly conserved positions [10,17]. Hence, hCG can stimulate TSH receptors to produce thyroid hormone and

suppress TSH levels. TSH levels increase gradually during the second and third trimesters, because the hCG levels are lower.

GTT is usually transient, has a short duration, and resolves spontaneously as the hCG levels decline [7]. Most patients with GTT do not require specific treatment, and it is not associated with unfavorable pregnancy or perinatal outcomes [5,18].

## Distinction between gestational transient thyrotoxicosis and Graves' disease

Most patients with GTT have no or mild symptoms of hyperthyroidism, such as palpitations only [3], whereas GD manifests as palpitations, anxiety, hand tremors, and heat intolerance [2]. In addition, accurate clinical history, physical examination, and, occasional ultrasonography can distinguish these two conditions. For example, the absence of a history of thyroid disease and clinical signs of GD, such as goiter and ophthalmopathy, may favor a diagnosis of GTT [19]. However, differentiating between GTT and GD is challenging when the clinical characteristics of GD are absent, because the manifestations of GTT are not always apparent [6]. Estimating thyroid stimulation directly using, for example, radioactive iodine uptake tests, or tests that examine the distribution of functional tissue using, for example, thyroid scintigraphy, is contraindicated during pregnancy. Essentially, GTT is nonautoimmune transient hyperthyroidism that occurs in normal pregnancies, which differentiates it from GD; therefore, when a diagnosis is ambiguous, determining the TSH receptor antibody (TRAb) level is indicated [20].

***Treated Graves' disease***

Between 26% and 44% of patients with treated GD have GTT [21,22]. As GTT occurs in 2–11% of women with normal pregnancies [4], the prevalence of GTT among pregnant patients with GD is much higher than that in normal pregnancies. This finding may be associated with the greater receptiveness of the thyroid of patients with GD to stimulation, because it is primed by TRAbs. A study reported that among patients with GD, the TRAb and hCG levels were higher in those with GTT compared with those without GTT [22]. When patients receive antithyroid drugs, evaluating the effects of pregnancy on the thyroid and on the course of GD is challenging. GD is aggravated during the first trimester, and ameliorates gradually during the latter half of pregnancy [21]. Moreover, hCG stimulation mildly aggravated thyrotoxicosis during early pregnancy in patients with GD who were near remission [23]. Greater thyroid hormone elevations occur during early pregnancy in many patients with GD [21], however, whether hCG or TRAb causes these elevations remains unclear. Evaluating the serum hCG and TRAb levels may help elucidate such patients' diagnoses. However, pregnancy profoundly affects the maternal immune system, leading to general immunosuppression (e.g., reduced helper T-cell function) [24], which reduces the TRAb levels [25]. A previous study showed that the TRAb levels did not increase during early pregnancy in women with confirmed GD who were in remission before pregnancy [23].

***New-onset Graves' disease during pregnancy***

Ide et al. [26] reported that among patients with thyrotoxicosis during pregnancy and postpartum, 7% had new-onset GD during pregnancy. The mechanism underlying the

development of new-onset GD during pregnancy is unclear; however, many immunological factors contribute to maternal autoimmunity. Thyrotoxicosis in a woman with no evidence of hyperthyroidism before pregnancy favors a GTT diagnosis rather than a GD diagnosis. Regarding the differential diagnosis of new-onset GD during pregnancy and GTT, Ide et al. [26] reported significant delays in the onset of thyrotoxicosis, significantly higher FT4 and FT3 levels, and higher FT3/FT4 ratios in new-onset GD. Moreover, these researchers used ultrasonography and found that the thyroid volume and blood flow were significantly greater in patients with GD than in those with GTT. However, the investigators suggested that these parameters may not be sufficiently sensitive to differentiate between GD and GTT and recommended determining the TRAb levels as a more sensitive and specific method. Physiological immunosuppression tends to suppress the TRAb levels during pregnancy, and they are often undetectable in patients with new-onset GD and in those whose GD is in remission [25]. Final diagnoses should be confirmed during patient follow-up; however, some patients' differential diagnoses may remain elusive.

***Thyroid-stimulating hormone receptor antibody-negative Graves' disease***

Thyroid autoantibodies are present in patients with GD, but not in those with GTT [20]; however, these autoantibodies are undetectable in some patients who appear to have typical GD. Some antibody-negative patients may have GD but remain undiagnosed as the antibody levels may be below the detection level initially, which is a consequence of pregnancy-related immunosuppression [25].

Besides, false-negative thyroid antibody results are always possible. First, second, and

third generation thyroid binding inhibiting immunoglobulin assays have been developed, and each new generation assay has greater sensitivity and specificity [27,28] (Table 1). Despite using the newest TRAb assays, sensitivity may vary according to the stage of the disease [23], and some patients with GD will test negative. However, some TRAb-negative patients develop TRAb-positive GD during follow-up [29]. Therefore, comparative follow-up studies are required. Furthermore, Nishihara et al. [29] reported that 4.5% of their patients with antibody-negative GD had activating mutations of the TSH receptor that caused diffuse thyroid enlargements and clinical or subclinical hyperthyroidism.

## Unusual clinical manifestations of gestational transient thyrotoxicosis

GTT is generally associated with subclinical or mild hyperthyroidism. However, some patients with GTT, including those with HG, gestational trophoblastic disease, and multiple pregnancies, have severe symptoms requiring treatment. Thyrotoxicosis in GTT occurs temporarily from 10–15 weeks of pregnancy, which corresponds with the peak serum hCG levels [6], but it can persist beyond 20 weeks of pregnancy, for example, during multiple pregnancies, and it can develop during and beyond the second trimester, for example, in patients with gestational diabetes mellitus (GDM) and mirror syndrome.

### *Hyperemesis gravidarum*

The incidence of HG is 0.3–1%, and it is a complication of early pregnancy characterized by persistent vomiting, >5% weight loss, ketonuria, electrolyte abnormalities, and dehydration [30]. GTT occurs in 30–60% of patients with HG [13,31–33]. The

mechanism underlying HG and the role of hyperthyroidism in HG are unclear. However, hCG may be involved in the pathogenesis of GTT and HG, because higher hCG levels are found in both conditions [34]. The hCG levels correlate positively with the vomiting severity and the degree of thyroid stimulation [32]. Sun et al. [31] reported that the overall incidence of GTT increased significantly if the serum hCG levels were >80,000 IU/L, subclinical GTT was present if the serum hCG level was 80,000–140,000 IU/L, and clinical GTT was present if the serum hCG level was >180,000 IU/L.

Patients with HG complicated by GTT usually complain of nausea, vomiting, and weight loss by 4–9 weeks of gestation, and they present with tachycardia, fine tremors, and mild proximal weakness. Patients with high serum FT3 levels present with shortness of breath, heat intolerance, and palpitations. Hyponatremia, hypokalemia, mild hyperbilirubinemia, and mild-to-moderate liver enzyme elevations are also described [35]. The most appropriate treatment for HG with GTT includes fasting and intravenous hydration to maintain the water and electrolyte balance, and thyroid function elevations should be conducted. Antithyroid drugs might be warranted for patients with severe clinical symptoms; treatment usually lasts for a few weeks, because thyroid function normalizes by the second trimester [6,7].

Given the relatively high incidence of GTT in patients with HG, thyroid function should be evaluated routinely to avoid unnecessary antithyroid drug therapy and to detect excessively high thyroid hormone levels [31].

***Gestational trophoblastic disease***

Gestational trophoblastic disease is a rare complication that ranges from hydatidiform

mole (HM) to choriocarcinoma, and HM, which is also known as a molar pregnancy, is the most common form. The incidence of HM in Europe and North America is approximately 0.1% of all pregnancies [36]. Molar pregnancies are present in 7% of patients with hyperthyroidism and rarely in patients with severe thyrotoxicosis [37]. Women with molar pregnancies may present with pathologically high hCG levels. The thyrotropic activity of hCG from HMs is augmented compared with that associated with hCG from normal placentas. Indeed, cyclic adenosine monophosphate (cAMP) production is exacerbated by hCG in the serum from women with gestational trophoblastic disease when it is incubated with Chinese hamster ovary cells transfected with the human TSH receptor [38]. The severity of thyroid disease in patients with HMs increases with age, parity, the beta-hCG level, and mole size [39].

Surgically removing the HM rapidly ameliorates hyperthyroidism and, if possible, surgery should occur during early pregnancy [40]. Nevertheless, uncontrolled hyperthyroidism may develop into a thyroid crisis or cause serious arrhythmias perioperatively [41]. Patients require close observation for the first 24–48 h postoperatively, preferably in a high-dependency unit. Further, to exclude the presence of persistent trophoblastic tissue, thyroid function and beta-hCG levels should be monitored regularly until the hCG levels normalize.

***Multiple pregnancies***

Grün et al. [42] reported that compared with single pregnancies, twin pregnancies were associated with more frequent and profound serum TSH level reductions. Moreover, they found that the mean peak serum hCG levels at 9–11 weeks were significantly higher in

twin pregnancies compared with those in single pregnancies (171,000 U/L vs 65,500 U/L), and that hCG levels >75,000 U/L lasted for <1 week in single and ≤6 weeks in twin pregnancies. Higuchi et al. [43] described a patient with GTT who had severe symptoms, and they suggested that the overproduction of hCG (359,900 mIU/mL at 12 weeks' gestation) caused by the triplet pregnancy led to severe GTT. Ogueh et al. [44] found that maternal thyroid activity levels increased with the fetal number. Figure 2 shows the median serum hCG levels by pregnancy type [45]. In multiple pregnancies, the peak hCG levels are significantly higher and the peaks are of much longer durations than those in single pregnancies [6,42]. Compared with single pregnancies, the placenta may produce larger amounts of hCG for longer periods during multiple pregnancies. Conversely, Sakaguchi et al. [46] reported that the serum hCG levels in multiple pregnancies did not correlate positively with the thyroid hormone levels and differed from the results from normal single pregnancies. These investigators suggested that hCG circulating during multiple pregnancies may comprise variants with lower levels of thyrotropic activity that were likely related to the molecular heterogeneity of hCG.

***Gestational diabetes mellitus***

GDM affects 2–5% of pregnant women [47]. Oguz et al. [48] reported a significantly higher frequency of GDM among women with GTT (13.4%) compared with that among healthy pregnant women without GTT (4%); patients with GTT had significantly higher hemoglobin A1c (HbA1c) levels at 6–12 weeks of pregnancy and the TSH levels correlated negatively with the HbA1c levels in the thyrotoxic state. Furthermore, Artner et al. [49] found that compared with women with healthy pregnancies, women with GDM

had similar serum hCG levels during the first trimester, their hCG levels increased from the twenty-fifth week of gestation until the end of the pregnancy, and they had significantly higher serum hCG levels after 30 weeks of gestation. A recent study's findings demonstrated that the serum beta-hCG levels in women with GDM increased with gestational age [50]. Hence, women with GDM may have GTT during the second or third trimester because of a potential association between the excessive production of hCG and low levels of progesterone production caused by reduced placental function [51]. Thyroid hormones may increase gluconeogenesis and glycogenolysis rates, elevate insulin degradation rates, increase the secretion of and exacerbate the effects of glucagon, and increase the plasma free fatty acid concentrations [52]. Therefore, GTT itself may adversely affect glucose tolerance until late pregnancy.

***Mirror syndrome***

Mirror syndrome is characterized by maternal edema, fetal hydrops, and placental hypertrophy [53]. The hydropic placenta is believed to cause mirror syndrome, and excessive shedding of the placental trophoblast and/or placenta-derived angiogenic factors are related to its etiology [53]. The hCG levels are often markedly higher in mirror syndrome [54]. Given that the placental trophoblast releases hCG, the hCG elevations could indicate the level of placental disturbance [55].

Some patients have mirror syndrome complicated by thyrotoxicosis [56,57], which may be caused by excessive hCG production, because abnormal hCG has an even greater thyroid-stimulating ability than normal hCG. Maternal symptoms of mirror syndrome are likely to emerge beyond the second trimester and disappear shortly after the fetal

symptoms have been successfully treated or the pregnancy has been terminated [58]. Therefore, the onset of thyrotoxicosis in this condition might be later than that in typical GTT. Assessing maternal hCG levels and thyroid function should be part of the evaluation of fetal hydrops associated with mirror syndrome.

***Familial nonautoimmune hyperthyroidism***

Rodien et al. [59] reported a patient with GTT who had similar hCG levels to those seen in normal pregnancies. The patient developed persistent thyrotoxicosis that required antithyroid drugs during pregnancy, and her condition improved rapidly postpartum. The researchers found a mutation in the gene encoding the TSH receptor that resulted in the replacement of a lysine residue with an arginine residue at position 183 (Lys183Arg) in the patient and her mother. The mutant receptor was more sensitive to hCG than the wild-type receptor; it caused a four-fold increase in cAMP production that increased the thyroid hormone level [60]. Subsequently, Coulon et al. [61] described another patient with prolonged and severe GTT whose TSH receptor gene sequence had a mutation that caused the replacement of lysine 183 with asparagine (Lys183Asn), resulting in greater sensitivity to hCG.

## Conclusions

As GTT and GD during pregnancy can show similar clinical symptoms, it is important to differentiate these diseases. However, gold standard investigative methods have not yet been established. Although GTT tends to be associated with subclinical or mild hyperthyroidism, it can lead to unusual manifestations, including a delayed onset, worse

symptoms, or a prolonged clinical course, in women with particular complications. Hence, thyroid function should be routinely tested and followed in patients with conditions likely to cause GTT.

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**Table 1.** Immunoassay methods for detecting/measuring thyroid-stimulating hormone receptor antibodies.

| Generation | TSHR | Phase | Technology | Tracer | Assay time | Procedure | Clinical sensitivity, mean (range) (%) | Clinical specificity, mean (range) (%) |
|---|---|---|---|---|---|---|---|---|
| First | Solubilized porcine | Liquid | RIA | Labelled bovine TSH | >1 day | Manual | 77.5 (52.2–94.0) | 99.2 (97.5–100.0) |
| Second | Immobilized porcine, recombinant human | Solid | RIA | Labelled bovine TSH | >3 h | Manual | 95.9 (85.5–100.0) | 97.9 (91.4–100.0) |
| Third | Immobilized porcine | Solid | ECLIA, FEIA, CLEIA | Labelled M22 | <30 min | Fully automated | 97.7 (96.0–100.0) | 99.5 (98.9–100.0) |

TSHR: thyroid-stimulating hormone receptor; RIA: radioimmunoassay; ECLIA: electrochemiluminescence immunoassay; FEIA: fluorescence enzyme immunoassay; CLEIA: chemiluminescent enzyme immunoassay; TSH: thyroid-stimulating hormone; M22: thyroid-stimulating human monoclonal antibody.

## Figure captions

**Figure 1.** The pattern of changes in thyroid function and human chorionic gonadotropin.

hCG: human chorionic gonadotropin; TSH: thyroid-stimulating hormone; T4: thyroxine; TBG: thyroxine-binding globulin.

**Figure 2.** Serum median human chorionic gonadotropin levels by pregnancy type.

hCG: human chorionic gonadotropin.

**Figure 1**

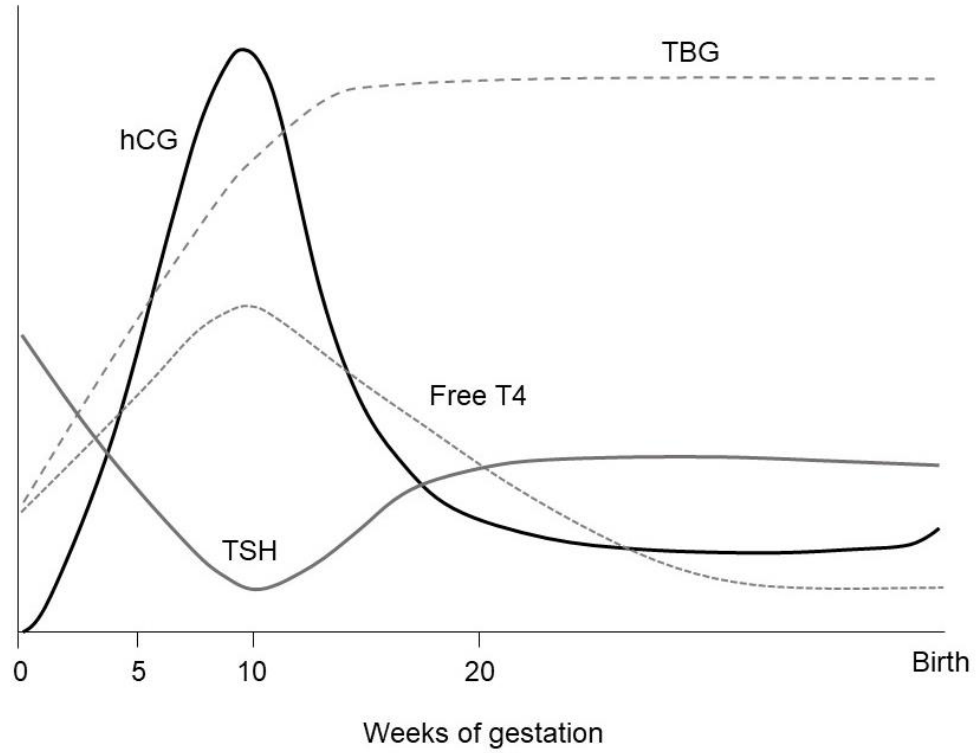


**Figure 2**